

## REMARKS

### STATUS OF THE CLAIMS

Claims 4, 6-9 and 16-18 were pending in this application. Claims 4 and 6-9 have been cancelled without prejudice. Claim 16 has been amended. New claims 19-29 have been added. Following entry of the amendments claims 16-29 will be pending and at issue.

### SUPPORT FOR AMENDMENTS TO THE CLAIMS

Support for the amendments to claim 16 can be found throughout the instant specification as filed, including at p. 4, lines 27-32 (referring to “region II which is complementary within the double-stranded structure is formed by two separate RNA single -strands”); p. 3, lines 17-25 (e.g., “interference effect mediated by the dsRNA”). Corresponding support for the amendment to claim 16 can also be found throughout the parent U.S. App. No. 09/889,802, filed on September 17, 2001, including at p. 4, lines 27-32; p. 3, lines 17-25. Similarly, corresponding support for claim 16 can further be found throughout the parent PCT WO00/44895 (PCT/DE00/00244) filed on January 29, 2000, including at p. 4, lines 27-32; p. 3, lines 17-25.

Support for the new claims 19-23 reciting linkage can be found throughout the instant specification as filed, including at p. 4, lines 34-39 to p. 5, lines 1-6; p. 5, lines 16-39 to p. 6, lines 1-7; p. 17, lines 9-27. Corresponding support for new claims 19-23 can also be found throughout the parent U.S. App. No. 09/889,802, including at p. 4, lines 34-39 to p. 5, lines 1-6; p. 5, lines 16-39 to p. 6, lines 1-7; p. 17, lines 9-27. Similarly, corresponding support for claims 19-23 can further be found throughout the parent PCT WO00/44895 (PCT/DE00/00244), including at p. 4, lines 34-39 to p. 5, lines 1-6; p. 5, lines 16-39 to p. 6, lines 1-7; p. 17, lines 9-27.

New claims 24, 25, and 26 recite the same limitations as were found in now cancelled claims 6, 8, and 9 that depended from now cancelled independent claim 4.

Support for the new claim 27 can be found throughout the instant specification as filed, including at p. 4, lines 27-32 (e.g., “A region II which is complementary within the double-stranded structure is formed by two separate RNA single strands”). Corresponding support for

new claim 27 can also be found throughout the parent U.S. App. No. 09/889,802, including at p. 4, lines 27-32. Similarly, corresponding support for claim 27 can further be found throughout the parent PCT WO00/44895 (PCT/DE00/00244), including at p. 4, lines 27-32.

Support for the new claim 28 can be found throughout the instant specification as filed, including at p. 4, lines 27-32 (referring to a complementary, double-stranded region II, and distinguishing between embodiments in which this region is which is “formed by two separate RNA single strands” or is formed “by autocomplementary regions”). Corresponding support for new claim 28 can also be found throughout the parent U.S. App. No. 09/889,802, including at p. 4, lines 27-32. Similarly, corresponding support for claim 28 can further be found throughout the parent PCT WO00/44895 (PCT/DE00/00244), including at p. 4, lines 27-32.

Support for the new claim 29 can be found throughout the instant specification as filed, including at p. 2, lines 11-21 (e.g., “It is believed that the particular activity of the dsRNA used in nematode cells is not due to the antisense principle, but possibly on catalytic properties of the dsRNA, or enzymes induced by it.”). Corresponding support for new claim 29 can also be found throughout the parent U.S. App. No. 09/889,802, including at p. 2, lines 11-21. Similarly, corresponding support for claim 29 can further be found throughout the parent PCT WO00/44895 (PCT/DE00/00244), including at p. 2, lines 11-21.

Thus, no new matter is added with any of the claim amendments or with any of the new claims.

#### **REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH**

Claims 4 and 6-9 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner stated that there is no support for a 21 base pair dsRNA having non-linked strands. *See Office Action*, p. 2. Applicants respectfully disagree with this rejection for reasons pointed out in the prior office action response and in various responses before that. However, without agreeing with the Examiner's rejection but to expedite prosecution of this application, Applicants have cancelled claims 4 and 6-9. Applicants reserve the right to pursue this cancelled subject matter in other applications. Thus, Applicants respectfully request withdrawal of this ground of rejection.

## REJECTIONS UNDER 35 U.S.C. § 102

Claims 4 and 6-9 are rejected under 35 U.S.C. § 102(b) as allegedly being unpatentable over Elbashir et al. (Nature 2001) and Tuschl et al. (WO 02/44321). Claims 4 and 6-9 are also rejected under 35 U.S.C. § 102(b) as allegedly being unpatentable over Crooke (US 6,107,094). Without agreeing with the Examiner's rejections but to expedite prosecution of this application, Applicants have cancelled claims 4 and 6-9. Thus, these rejections are rendered moot and Applicants request they be withdrawn.

## REJECTIONS UNDER 35 U.S.C. § 103

Claims 16-18 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Agrawal et al. (WO/ 94/01550). Applicant traverses this ground of rejection.

Independent claim 16 recites the following:

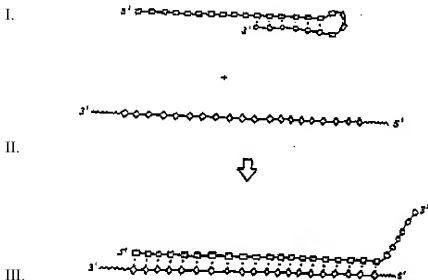
16. An isolated oligoribonucleotide consisting of **two separate complementary RNA single strands forming a double-stranded structure (dsRNA)**, wherein said separate RNA strands are chemically linked, wherein the dsRNA is 21 base pairs in length, wherein the dsRNA does not comprise a full length RNA transcript of a mammalian target gene, wherein one strand of the dsRNA is complementary to less than the full length of an RNA transcript of said mammalian target gene, and **wherein the dsRNA specifically inhibits the expression of said mammalian target gene using dsRNA-mediated interference.**

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. However, Agrawal fails to teach at least the portions of claim 16 shown in bold font above.

### A. Two Separate Strands forming Double-Stranded Structure (dsRNA)

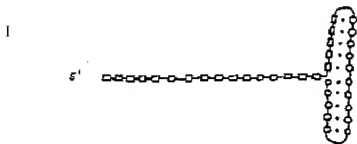
First, Agrawal teaches self-complementary antisense oligoribonucleotides, and does not teach *dsRNAs* consisting of two separate complementary single strands forming a double-stranded structure. Agrawal teaches an oligoribonucleotide useful for antisense therapeutics that has the following two regions: (i) a target hybridizing region and (ii) a self-complementary region. See Agrawal et al., page 8, lines 22-24. The target hybridizing region is the region of the antisense molecule that hybridizes to the target RNA. Agrawal explains that the self-

complementary region of the antisense molecule contains a sequence that is complementary to other ribonucleotides in that same molecule (e.g., other nucleotides in the self-complementary region itself, in the target hybridizing region, or both). *See id.* at page 15, lines 1-6. Thus, these two regions are within the same *single antisense oligoribonucleotide strand that folds back on and hybridizes to itself*, forming a hairpin loop or hammer-like structure. *See id.* at page 15, lines 9-11. This is illustrated in FIG. 1 of Agrawal, as reproduced below (with added Roman numeral labels):



Molecule I is the single antisense strand that has folded back on itself to form a loop, molecule II is the target RNA molecule (e.g., the target of the antisense strand I), and molecule III illustrates molecules I and II hybridized. *See also* Agrawal, p. 8, line 22 to p. 9, line 18 (explaining FIG. 1 in detail). As stated by the Examiner regarding antisense strand I, the small circles represent the self-complementary region and the small squares represent the target hybridizing region. The hairpin loop at the right of molecule I is formed by the self-complementary region (small circles) folding back and hybridizing to another part of the same molecule (in this case, to the target hybridizing region (small squares)). This one antisense

strand (molecule I) that has folded back on itself to form a loop is not equivalent to the claimed double-stranded RNA formed of *two separate single strands*. The same is true for molecule I when it is in a hammerhead formation, as shown in reproduced FIG. 2 of Agrawal below (with added Roman numeral label):



Again, this is a single antisense strand (like the hairpin molecule I) that has folded back on itself, as opposed to being *two separate RNA strands that are hybridized to form a dsRNA*. One having ordinary skill in the relevant arts would not read Agrawal to suggest an oligoribonucleotide consisting of *two separate complementary RNA single strands that form a double-stranded structure*.

In the Office Action of September 23, 2008 (p. 9-10), the Examiner equated the chemical linkage of the strands recited in claim 16 with Agrawal's description of a polyethylene glycol that links the self-complementary region to the target hybridizing region of the antisense oligoribonucleotide. *See* Agrawal, p. 15, line 26 to p. 17, line 12. However, Agrawal at most discloses a linker that connects two regions of a *single antisense strand*, but fails to disclose *two separate RNA single strands that are a chemically linked*, as claimed. The instant specification, at Example 2, explains that the dsRNA is "stabilized by *chemically linking the single strands*." Specification, p. 19, lines 17-18 (emphasis added). Agrawal does not disclose or suggest using a chemical linker to connect two single RNA strands, as required by claim 16.

Furthermore, the interpretation of the claimed invention as including a self-complementary structure, as opposed to the claimed two separate RNA strands forming a

dsRNA, is not consistent with the instant specification. MPEP § 2111 states that “[d]uring patent examination, the pending claims must be ‘given their broadest reasonable interpretation *consistent with the specification.*’” MPEP § 2111(emphasis added) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005)). The specification refers to the complementary, double-stranded region II of a dsRNA, and explains that it can be 1) “formed by two separate RNA single strands” or it can be 2) formed by self-complementary or “autocomplementary regions,” such as in an “RNA hairpin loop.” *See* Specification, p. 4, lines 27-32 and p. 8, lines 8-14. Claim 2 is drawn to description 1), as is made clear by the language of claim 16 specifically referring to the “two separate RNA single strands” that form the double-stranded structure. Thus, the claim interpretation consistent with the specification is not an autocomplementary hairpin loop, but is a separate-stranded embodiment that is not taught by or rendered obvious by Agrawal.

#### **B. dsRNA-Mediated Interference**

Second, and as a separate basis for distinction, Agrawal also does not disclose a dsRNA that specifically inhibits the expression of a target gene *using dsRNA-mediated interference*. Agrawal describes the “*antisense oligonucleotide based therapeutic principle*” and problems with *antisense oligonucleotide* stability, ultimately concluding that “the prior art is devoid of any teaching or suggestion about using self-complementary oligonucleotides in the *antisense oligonucleotide therapeutic approach*.” Agrawal, p.1, line 10 to p. 4, line 22 (emphasis added). Agrawal explains that he is attempting to solve these prior art problems with “therapeutic agents used in the *antisense oligonucleotide therapeutic approach*” that are resistant to degradation. *Id.* at p. 5, lines 1-12 (emphasis added). Agrawal continues to explain throughout his description how his antisense strand that folds back on itself is superior to the prior art antisense oligoribonucleotides.

While Agrawal describes an antisense therapeutic approach, Agrawal does not describe “dsRNA-mediated interference,” as one of ordinary skill in the art would understand this term. MPEP § 2111 states that the “broadest reasonable interpretation of the claims must be *consistent with the interpretation that those skilled in the art would reach*” (emphasis added). *See also In*

*re Cortright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999). One of ordinary skill in the relevant art would not interpret dsRNA-mediated interference to be equivalent to or rendered obvious by the antisense oligonucleotide-based therapeutic principle disclosed by Agrawal.

Accordingly, Agrawal does not disclose each and every element of the independent claims, nor the claims that depend therefrom. Thus, withdrawal of this rejection is respectfully requested.

### **C. Examples of Additional Claim Elements not Taught by Agrawal**

Agrawal also fails to teach the element recited in new claim 27, “wherein one of the single strands is complementary to the other of the single strands, wherein the two separate single strands hybridize to each other to form the double-stranded structure, and wherein the one of the single strands is also chemically linked to the other of the single strands.” Agrawal discloses at most a single antisense strand that is *complementary to itself*, but does not disclose *one single strand that is complementary to another single strand*. Agrawal further discloses at most an antisense strand that *hybridizes to itself*, but does not disclose *two separate single strands hybridize to each other*. In addition, Agrawal discloses at most a linker *between two regions of a single strand*, but does not disclose *one single strand that is also chemically linked to another single strand*. Thus, Agrawal does not disclose the element recited in claim 27.

Agrawal also fails to teach the element recited in new claim 28, “wherein each of the single strands is complementary to the other of the single strands, and neither is autocomplementary.” Agrawal discloses at most a single antisense strand that is *self-complementary or autocomplementary*, but not a dsRNA having single strands complementary to each other and that are not autocomplementary. Thus, Agrawal does not disclose the element recited in claim 28.

Agrawal also fails to teach the element recited in new claim 29, “wherein the dsRNA-mediated interference occurs due to enzymes induced by the dsRNA that cause the inhibition of expression of the target gene.” Agrawal discloses at most the antisense oligoribonucleotide principle, and does not disclose dsRNA-mediated interference that occurs *due to enzymes*

*induced by the dsRNA* that cause the inhibition of expression of the target gene. Thus, Agrawal does not disclose the element recited in claim 29.

Accordingly, Agrawal does not disclose each and every element of at least dependent claims 27-29. Applicant that all of the claims, including claims 27-29, are in allowable form.



### CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (650) 335-7185.

Respectfully submitted,

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